Ann R Coll Surg Engl 1998; **80**: 313–315

CURRENT STATUS AND FUTURE PROSPECTS

Pancreas transplantation

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Diabetes mellitus is the principal cause of kidney failure and blindness in adults, and leads to more cases of amputations and impotence than any other disease. It is one of the most common chronic diseases of childhood. In the United States, diabetes costs $138billion each year, that is one out of every $7 spent on health care. The aim of pancreas transplantation is to improve quality of life of patients with type I insulin-dependent diabetes mellitus (IDDM) and to ameliorate secondary complications by establishing an insulin-independent euglycaemic state. This is achieved by engrafting insulin-producing β cells in the islets of Langerhans.

IDDM includes not only abnormal glucose metabolism but also specific microvascular complications such as retinopathy, nephropathy and neuropathy. Over the last 15 years, it has become increasingly evident that the microvascular complications of diabetes mellitus result from hyperglycaemia. Exogenous insulin therapy prevents acute metabolic decompensation and, when delivered so as to achieve near normal glucose concentrations, reduces the frequency of many complications. Even in well-controlled patients, exogenous insulin administration does not achieve the level of control effected by endogenous insulin secretion, which responds to moment-by-moment changes in glucose concentration. Pancreas transplantation is the only treatment for IDDM that is able to induce insulin independence consistently and which normalises glycosylated haemoglobin.

Patients who can be considered for a pancreas transplant fall into these categories:

1 *Pancreas after kidney (PAK).* Had a previous kidney transplant, and are already on antirejection drugs.
2 *Simultaneous pancreas-kidney (SPK).* Have failed or failing kidneys, and need a kidney transplant. Such patients are on dialysis, or will soon need dialysis unless a kidney transplant is carried out first. In such patients, a kidney and pancreas can be transplanted simultaneously from a cadaver donor.
3 *Pancreas transplant alone (PTA).* Need only a pancreas transplant. An individual whose kidneys have not failed can receive a pancreas transplant alone. Diabetic complications such as neuropathy must be present, or there must be extreme difficulty with diabetic control. This restriction is imposed because of the need for immunosuppressive drugs.

Patient selection is aided by a comprehensive multidisciplinary pretransplant evaluation, with additional work-up according to the specific problems of each patient. The evaluation confirms the diagnosis of IDDM, determines the patient's ability to tolerate a major operation which is based primarily on the patient's cardiovascular status, establishes the absence of any exclusion criteria and documents endstage organ complications for future tracking after transplantation. In a suitable candidate, the evaluation is also used to determine the type of pancreas transplantation, based principally on the degree of nephropathy. The degree of renal dysfunction, creatinine clearance < 20 ml/min, is used to select patients for SPK *versus* PTA (creatinine clearance > 70 ml/min). If the creatinine clearance is 20–70 ml/min the patient can be offered a pre-emptive kidney transplant.

The selection criteria for cadaver pancreas donors are similar to those for other solid organs. Specific criteria depend on donor pancreatic function. A history of diabetes mellitus or acute necrotising pancreatitis and chronic history of pancreatitis are obvious contraindications. In donors with a reported history of pancreatitis, it is always worthwhile examining the pancreas to assess suitability at the time of procurement. It should be remembered that, after brain death, serum amylase levels are often high in the absence of pancreatitis, and hyperglycaemia may occur in the absence of diabetes. Donor age is very important; if the donor age is over 45 years, the risk of graft thrombosis in all three categories is increased.

Only a 0 to 1 antigen mismatch has a similar benefit in any type of pancreas transplant. Therefore most centres do not use matching. The quality of the donor is more important than the quality of the match.

The immunosuppression for pancreas transplantation is similar to that for other solid organs. The idea is to maximise the immunosuppressive effects and minimise immunodeficient complications and toxicity by employing multiple agents at low doses. Since the mid-1980s, almost every programme has used cyclosporin in combination with azathioprine and prednisone for maintenance immunosuppression; most (>85%) also use anti-T-cell agents for induction; however, there is a recent change in practice to no induction at all. Recently, several institutions have achieved promising results using tacrolimus instead of cyclosporin for maintenance therapy. It is currently the primary immunosuppressant in 40% of pancreas transplants. In addition, azathioprine is being replaced by myophenolate mofetil (MMF).

Although transplantation requires a life-long commitment to immunosuppression, most diabetic patients find that they have fewer dietary and activity restrictions and a much better quality of life after pancreas transplantation. There is no evidence that immunosuppressive drugs are associated with any more complications over a 20-year period than is diabetes. Early pancreas transplantation can prevent secondary complications and, even when performed late, has been shown to improve nerve damage caused by diabetes. It would be reasonable for a person with diabetes to choose to have a pancreas transplant with long-term immunosuppression over choosing a lifetime with diabetes.

Rejection is the major cause of graft loss owing to difficulties in its early detection. While rejection rates used to be 60%, a number of centres are reporting figures of 10–40%. Transplantation of a pancreas and a kidney from the same donor allows manifestation of kidney allograft rejection to guide treatment; kidney graft rejection is believed to precede or occur concurrently with pancreas rejection. Urinary drainage of exocrine secretions enables direct monitoring of exocrine function by urinary assays; urinary amylase and cytology have been used as non-invasive markers of early rejection. Currently, non-invasive methods are not sufficiently accurate to replace histopathological examinations. Open biopsy is, however, seldom required, because safe cytoscopic and percutaneous biopsy techniques of the pancreas allograft have been developed. Many centres treat patients relying on biopsy-proven rejection, especially when enteric drainage is used.

Other causes of pancreas graft loss include vascular thrombosis which may occur, in part, because of the low microcirculatory flow through the pancreas and when the age of the donor is >45 years, but can also accompany pancreatitis or rejection. This is the most common cause of non-immunological graft loss. It is 5% in SPK and 12% in PTA. Hyperamylasaemia is common after transplantation and may be either asymptomatic or indicative of symptomatic pancreatitis. Patients with 'diabetic' neurogenic bladder can develop 'reflux pancreatitis' from inadequate bladder emptying. Surgical problems related to exocrine pancreatic drainage and allograft pancreatitis usually result from technical failure such as leak, fistula, or infection leading to fluid collections, pseudocysts or abscesses surrounding the pancreatic graft.

The bladder drainage technique, where the pancreatic secretions are drained into the bladder, is the most commonly used procedure (>80%). Recently, and because of the metabolic and urological complications associated with bladder drainage, enteric drainage with systemic venous drainage has become popular. A few centres have adopted enteric drainage with venous portal drainage.

Results

From 1996 to date over 10 000 pancreas transplantations have been performed worldwide, most in the last 10 years. According to the United Network for Organ Sharing (UNOS) Registry established in 1987:

- 84% of pancreas transplantations were SPK;
- 8% were performed as PAK;
- 6% were performed as a solitary transplantation PTA;
- 2% were performed in conjunction with a single organ transplantation other than the kidney or with multiple organs.

The results of pancreas transplantation have improved progressively since the introduction of cyclosporin and, more recently, tacrolimus, and the refinement of surgical techniques. In an analysis of 4500 cadaver donor cases reported worldwide between 1987 and 1996, the overall 1-year patient survival rate was 92% and the 1-year insulin-dependent rate was 79%. The 1-year kidney graft survival rate was 70% in Europe, 78% in the USA and 75% in the rest of the world. In the last decade, operative mortality has been 1–3% in most established centres.

In addition to correcting the metabolic disorder and freeing the patient from exogenous insulin therapy, there is evidence that pancreas transplantation has a beneficial effect on the course of secondary diabetic complications. In some studies with follow-up of 4 years or more after successful pancreas transplantation, stabilisation of retinopathy was better than that observed in patients followed for the same period of time but whose pancreas transplants had failed.

Both prospective and cross-sectional studies have suggested that pancreas transplantation prevents recurrence of diabetic nephropathy in a newly transplanted kidney, and studies have reported improved motor and sensory nerve function as assessed by nerve conduction velocity in pancreas–kidney transplant recipients when compared with recipients of kidney transplants alone or patients with pancreas graft failure. Studies of autonomic function after pancreas transplantation are less clear. In some studies, pancreas transplantation was associated with greater improvements in autonomic symptoms, even if they were accompanied by little objective evidence of change.

The increase in success rates has led to increasing interest in PTA in non-uraemic patients. More than 850 PTA have been carried out so far worldwide. As recently as 1996 there was a marked difference in the 1-year graft survival between SPK (79%), PAK (60%) or PTA (57%). The main reason is the high incidence of rejection; the incidence of late acute rejection being 7% in SPK; 25% in PAK and 41% in PTA.

Studies are unanimous in finding that patients with successful transplants rate their lives better after transplantation than before. The effect of a double transplant in uraemic diabetic patients can be dramatic; patients rate their quality of life higher than diabetics who receive a kidney transplant alone.

The future of pancreas transplantation

The advances in immunosuppressive strategies and diagnostic technology will improve the good results already achieved with pancreas transplantation. Further documentation of the long-term benefits and effects of pancreas transplantation may lead to wider availability and acceptance. Effective control of rejection with earlier diagnosis or better prevention may soon permit solitary pancreas transplantation to become an accepted treatment option in diabetic patients without advanced secondary complications of diabetes. Although there is significant morbidity after pancreas transplantation, this is usually manageable without adversely influencing the outcome. Other strategies for the treatment of IDDM are being actively investigated, including islet cell and fetal pancreas transplants, xenogenetic islets, gene therapy, implantable insulin pumps and biohybrid artificial pancreas units. Although any or all of these methods may have a role in the treatment of IDDM in the future, it will be difficult for these alternative strategies to improve on the metabolic efficiency of vascularised pancreas transplantation. With the improvement in quality of life and the potential reversing effect on diabetic complications, pancreas transplantation may become a more common transplant procedure and could become the treatment of choice for IDDM.

Further reading

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Received 23 April 1998